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(71) Demandeur/Applicant:
KNOLL AKTIENGESELLSCHAFT, DE

(72) Inventeurs/Inventors:
ROSENBERG, JORG, DE;
BREITENBACH, JORG, DE;
LIEPOLD, BERND, DE

(74) Agent: ROBIC

(54) Titre : PREPARATIONS SOLIDES CONTENANT DE LA PAROXETINE
(54) Title: SOLID PREPARATIONS CONTAINING PAROXETINE

(57) Abrégé/Abstract:
The invention relates to solid or semi-solid preparations of paroxetine or one of the physiologically acceptable salts thereof in the form of a molecular-disperse distribution of paroxetine in a pharmaceutically acceptable matrix material.

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(71) Anmelder *(für alle Bestimmungsstaaten mit Ausnahme von US)*: **KNOLL AKTIENGESELLSCHAFT** [DE/DE]; D-67061 Ludwigshafen (DE).

(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)*: **ROSENBERG, Jörg** [DE/DE]; Bruchstrasse 29, D-67158 Ellerstadt (DE). **BREITENBACH, Jörg** [DE/DE]; Hans-Sachs-Ring 95A, D-68199 Mannheim (DE). **LIEPOLD, Bernd** [DE/DE]; U1,8, D-68161 Mannheim (DE).

(74) Anwalt: **KINZEBACH, Werner**; Reitstötter, Kinzebach & Partner, Postfach 86 06 49, D-81633 München (DE).

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Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

WO 01/01956 A3

(54) Title: SOLID PREPARATIONS CONTAINING PAROXETINE

(54) Bezeichnung: FESTE PAROXETIN ENTHALTENDE ZUBEREITUNGEN

(57) Abstract: The invention relates to solid or semi-solid preparations of paroxetine or one of the physiologically acceptable salts thereof in the form of a molecular-disperse distribution of paroxetine in a pharmaceutically acceptable matrix material.

(57) Zusammenfassung: Die Erfindung betrifft feste oder halbfeste Zubereitungen von Paroxetin oder einem seiner physiologisch akzeptablen Salze in Form einer molekulardispersen Verteilung des Paroxetins in einem pharmazeutisch akzeptablen Matrixmaterial.

SOLID PREPARATIONS CONTAINING PAROXETINE

The present invention relates to solid or semisolid preparations of paroxetine or one of its physiologically active salts in the form of a molecular dispersion in a pharmaceutically acceptable matrix material. The invention further relates to a process for producing such preparations.

Paroxetine is the generic name for (-)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)piperidine, which is described, for example, in US-A 4 007 196.
Paroxetine belongs to the class of 5-hydroxytryptamine inhibitors and is used as antidepressant.

Because of its basicity, paroxetine is employed in the form of its acid addition salts for therapeutic use, in particular in the form of the particularly physiologically acceptable hydrochloride. However, paroxetine hydrochloride anhydrate shows a tendency to polymorphism. Thus, DE-C 196 03 797 describes four polymorphic forms of paroxetine hydrochloride anhydrate. Polymorphic forms are, however, problematical for therapeutic use since different polymorphs may have different solubilities and consequently differences in the bioavailability.

One possible solution to the polymorphism problem is to prepare the active ingredient in amorphous form. Thus, WO 99/16440 describes the production of amorphous, i.e. noncrystalline, paroxetine hydrochloride formulations by dissolving in a hydroxyl-containing compound such as ethanol and then removing this compound. Likewise, EP-A 0 810 224 describes the production of amorphous paroxetine hydrochloride by dissolving the active ingredient in water or a lower alcohol and then removing the solvent, for example by spray drying.

Dispersions, i.e. homogeneous microdisperse phases, of two or more solids, and the special case of "solid solutions" (molecular dispersion systems), and their use in pharmaceutical technology are generally known (cf. Chiou and Riegelman, J. Pharm. Sci., 60, 1281-1300 (1971)).

WO 99/00131 describes the production of solid dispersions of substances of low solubility in water using a solvent process or a melt process. This makes it possible, for example, to produce a solid dispersion of paroxetine hydrochloride in a solid carrier material by melting the free paroxetine base in the presence of

the carrier material, and then passing dry hydrogen chloride gas through the melt. The melt is then cooled to room temperature, for example by leaving to stand overnight, and is ground. However, the procedure described in this document is likely to be confined to the laboratory scale, and is still unsatisfactory in relation to the homogeneity of the mixtures. An additional factor is that the hydrogen chloride gas is very chemically reactive and may react with the excipients and form toxicologically unacceptable products.

EP-A 665 009 discloses the possibility of altering the crystalline state of active ingredients by processing in an extruder, the active ingredients being processed essentially without other excipients.

In addition, EP-A 760 654 discloses the possibility of producing acid addition salts directly by a melt extrusion process by reacting the free base in the presence of a salt.

WO 99/26625 discloses paroxetine formulations in which the active ingredient is dissolved in a copolymer and mixed with a molten polymer. Formulations of this type can also be extruded. However, such formulations are prone to recrystallization, because of the use of a cosolvent.

It is an object of the present invention to find improved preparations of paroxetine and its physiologically acceptable salts which, on the one hand, help to avoid the polymorphism problem, but, on the other hand, also have an improved solubility and storage stability for the active ingredient paroxetine which is of low solubility per se. It was a further object of the invention to provide a simplified process for producing such preparations.

We have found that this object is achieved by solid preparations of paroxetine and its physiologically acceptable salts in which the active ingredient is embedded as a molecular dispersion in a pharmaceutically acceptable carrier material which comprises a completely synthetic polymer having a glass transition temperature of >90°C.

The preparations may also be semisolid, although solid forms are preferred.

Suitable pharmaceutically acceptable salts of paroxetine are not only salts such as, for example, the fumarate or the maleate but also, in particular, the hydrochloride and the corresponding hydrochloride anhydrate.

Pharmaceutically acceptable matrix or carrier materials which are suitable in principle are all materials which can be processed by a melt process to give a homogeneous matrix with the active ingredient.

Suitable matrix polymers have a glass transition temperature of >90°C, preferably >90 to 110°C, in the anhydrous state and are completely synthetic polymers. Particularly suitable ones are melt-processable water-soluble polymers such as the homo- or copolymers of N-vinylpyrrolidone with Fikentscher K values in the range from 19 to 100.

Preferred matrix materials are polyvinylpyrrolidones or copolymers of N-vinylpyrrolidone and vinyl acetate such as VP/VAc 60/40 (copovidone).

It is also possible to add to the matrix conventional pharmaceutical excipients such as bulking agents, release agents, disintegrants, stabilizers, flavor-improvers, antioxidants or colors.

The novel preparations may contain paroxetine or one of its salts in amounts of from 0.1 to 50% by weight, preferably 5 to 30% by weight, based on the total weight of the preparation.

The novel preparations are preferably produced by a melt process, in particular by producing and processing the melt using an extruder.

Production can take place by initially producing a powdered premix of all the starting materials and introducing it into an extruder. This premix is processed to a homogeneous melt by introducing shear forces and thermal energy and is subsequently shaped. The melt is preferably produced at temperatures in the range from 80 to 100°C, preferably 80 to 150°C. It is also possible initially to melt only the matrix materials and then to meter the active ingredient in through suitable devices.

The extruder employed is preferably a corotating twin screw extruder. The homogeneous melt produced in this way can either be extruded through a die or a breaker plate, or else be conveyed through the open extruder head and, in this case, where

appropriate, be conveyed directly as granules through grinding elements disposed in the screw channel. The shaping can also take place by conventional pelletizing techniques, for example by hot cut or cold cut or using compressed air.

The shaping of the extruded and still plastic melt can also take place by passing the extrudate between counter-rotating calender rolls with depressions, in which case tablet shapes can be produced directly.

The novel preparations are preferably produced in the absence of solvents. However, if the starting materials contain solvents, these can be removed in the extruder by applying a vacuum. It is also possible in this way to remove water of crystallization if still present in the active ingredient employed. Suitable solvents are, for example, volatile organic solvents or water.

In a particularly preferred embodiment of the invention, the paroxetine salt is produced by processing the free paroxetine base together with a compound which is suitable for forming an appropriate acid addition salt, and the appropriate matrix materials, by a melt extrusion process in an extruder. Ammonium chloride is preferably employed as salt-forming component to produce the corresponding hydrochloride.

Preferred novel preparations have instant release of the active ingredient. Instant release means that the release of active ingredient measured in a paddle apparatus at pH 1.2, 50 rpm and 37°C, is at least 80% after 30 min.

The novel solid preparations comprise the active ingredient embedded in the form of a molecular dispersion in a matrix. The matrix behaves like a true solvent, i.e. every active ingredient molecule is surrounded by molecules of the matrix materials. This is visually evident from the transparency of the resulting cooled melts. This state of molecular dispersion in the cooled melt is moreover thermodynamically stable, i.e. no recrystallization processes occur. As a consequence of the molecular dispersion of the active ingredient in the matrix, the preparations show instant and uniform release of active ingredient. The active ingredient is essentially released from the solidified melt after 30 min.

Examination of the extruded melts by differential scanning calorimetry (DSC) no longer shows any melting signals in the region of the active ingredient melting point. In the case of polymeric matrix materials, only broad polymer glass transition steps are evident.

It is also possible according to the invention to employ amorphous paroxetine or its salts. The amorphous forms dissolve more quickly in the matrix because no lattice energy must be supplied for the melting. This makes processing at lower temperatures possible.

The novel preparations are moreover stable to uptake of moisture, i.e. no recrystallization occurs. This is all the more surprising since extremely hydrophilic polymers are employed. The products also show improved storage stability. Surprisingly, paroxetine can be extruded without decomposition despite the sensitive acetal group. This is all the more surprising since PVP and its copolymers have an acidic pH.

The novel preparations can be obtained in the form of granules and be used as such to fill capsules or be compressed to tablets or, as described above, be calendered directly to tablet form or else be used as semisolid preparations to fill capsules.

Examples

Powdered premixes of the following composition were processed, employing in each case anhydrous paroxetine hydrochloride:

Example 1

Paroxetine hydrochloride	30% by weight
copovidone	70% by weight
finely dispersed silica (1% by weight based on active ingredient/polymer)	

The powdered premix was melted and extruded in a twin screw extruder with a screw diameter of 16 mm at a material temperature of 145°C. The resulting slightly yellowish transparent melt remained transparent even after cooling. Even after storing per 9 months at 40°C and at 45% relative humidity, the transparency was retained.

Example 2

A mixture as in Example 1 was extruded analogously through a round-section die with a diameter of 3 mm. To determine the active ingredient release, the cooled, transparent extrudate was divided into pieces weighing 133 mg (paroxetine hydrochloride content of 40 mg). The release was determined by the USP XXII method in a paddle apparatus at pH 1.2, 50 rpm and 37°C:

Time [min]	Active ingredient release [% by weight]
0	0
5	19
10	42
20	82
30	96
60	99

Example 3
Production of tablets

Biconvex tablets with a diameter of 9 mm and a weight of 200 mg were produced by compressing the starting materials in a conventional tablet press (Fette E2 eccentric press) under a pressure of 6.5 kN. The tablet had the following composition:

paroxetine hydrochloride extrudate from Ex. 1	38% by weight
microcrystalline cellulose	15% by weight
calcium hydrogen phosphate (anhydrous)	35% by weight
Na croscarmellose	10% by weight
highly disperse silica	1% by weight
magnesium stearate	1% by weight

The tablets had completely disintegrated in water at 37°C in 5 min.

0480/01221

We claim:

1. A solid or semisolid preparation of paroxetine or one of its physiologically acceptable salts in the form of a molecular dispersion of paroxetine in a pharmaceutically acceptable matrix material which comprises a completely synthetic polymer having a glass transition temperature of >90°C.

2. A preparation as claimed in claim 1, comprising paroxetine hydrochloride.

3. A preparation as claimed in either of claims 1 or 2 having an active ingredient release of at least 80% after 30 min.

4. A process for producing a preparation as claimed in any of claims 1 to 3, which comprises the paroxetine or one of its salts and the matrix material being mixed to give a homogeneous melt in an extruder and subsequently being shaped.

5. A process as claimed in claim 4 for producing a paroxetine hydrochloride preparation, wherein paroxetine is processed with ammonium chloride and the matrix materials to give a homogeneous melt.

6. A process as claimed in claim 5, wherein amorphous paroxetine or one of its physiologically acceptable salts is employed.